Achieving Therapeutic Success in Alzheimer’s Disease: The Case for Refining our Approach

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Welcome to Vancouver….eh !

NB Cross the street with care on Sunday !
Disclosure

- 2012-16  UBC service agreements, or sponsored clinical trials;
  - Eli Lilly, Kyowa Kirin, GE Healthcare, Biogen, Arena, Roche/Genentech, Merck, Eisai, Baxter, Tau Rx

- Peer Reviewed Research Support:
  - NIA, CIHR, Brain Canada, Weston Foundation
  - PI Alzheimer Disease Study Cooperative (From April 1, 2016)

- 2009-2011, on leave from UBC and employed at Bristol-Myers Squibb Company in CT, USA
  - VP and Therapeutic Area Head, Neuroscience Global Clinical Research
Objectives

- To review the landscape and trajectory of Alzheimer’s disease therapeutic development
- To provide some reflections on progress to date
- To offer a viewpoint on how we can refine our approach to increase likelihood of success
Global Viewpoint on Therapeutic Goals

- NAPA: Prevent and effectively treat AD by 2025.
- G8 Global Action Against Dementia: Summit declaration
  - The ambition to identify a cure or a disease-modifying therapy for dementia by 2025
  - We will increase the number of people in dementia related research studies
- WHO 2012:
  - Efforts to improve the quality and availability of care, and to seek for a cure, should be coupled with urgent investment in primary prevention measures.

Pipeline of antidementia drugs vs cancer

- 3.8% drugs in discovery vs 31% cancer
- 1.2% in phase 3 compared to 24% cancer

Pipeline Analysis (2000 trials all sources over 20 years)

- 900 registered compounds commercial R&D source
- Of these 197 in active development
- 129 terminated, withdrawn or suspended
- Remainder non active, presumed terminated or discontinued
The Need to Learn from Clinical Trials:

- **For terminated trials only 45% provided a reason,**
  - most commonly recruitment problems
- **Rationale for d/c products in only 26%**
  - most common safety and efficacy

- Insufficient reporting of trial outcomes
- Inability to learn quickly from failures across classes
- Needless exposure of trial participants to products having low probability of success
- Need for clinical trials data sharing for modelling, simulation and hypothesis generation
To achieve a cure:

- 30 new therapeutic drugs need to reach early clinical testing
- 3 diverse classes of drug targets
- 12 new drugs advancing from first in man to phase 2 trials

A massive underestimate?
Solanezumab: Phase 3 Results
Expedition 1 Trial: Mild to Moderate AD

ADAS-cog 11

ADCS-ADL

http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf
### Solanezumab: Expedition Trials: Phase 3 Results: Subanalysis of Mild AD (MMSE 20-26)

<table>
<thead>
<tr>
<th></th>
<th>EXP1 overall</th>
<th>EXP1 mild</th>
<th>EXP2 overall</th>
<th>EXP2 mild</th>
<th>Pooled overall</th>
<th>Pooled mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ADAScog_{11}</td>
<td>.312</td>
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<td>.060</td>
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<tr>
<td>ADAScog_{14}</td>
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<td>.002</td>
<td>.004</td>
<td>.099</td>
<td>.002</td>
<td>.001</td>
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<td>Functional</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ADCS-ADL</td>
<td>.931</td>
<td>.302</td>
<td>.062</td>
<td>.076</td>
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<td>.057</td>
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<tr>
<td>ADCS-iADL</td>
<td>.919</td>
<td>.319</td>
<td>.080</td>
<td>.029</td>
<td>.250</td>
<td>.045</td>
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</table>

n = 2,052

http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf
Aducanumab: Phase 1 ‘Multiple Ascending Dose’ PRIME Study in Prodromal or Mild AD

**Design**

- Randomized
  - Pooled Placebo 40
- Dosed
  - 1 mg/kg 21
  - 3 mg/kg 32
  - 6 mg/kg 30
  - 10 mg/kg 32
- Discontinued treatment
  - Adverse event 9
  - Lost to follow-up 3
  - Disease progression 0
  - Consent withdrawn 0
  - Investigator decision 1
  - Death 1
  - Other 3

**MMSE**

Adjusted mean change from baseline (± SE)

**CDR SB**

Adjusted mean change from baseline (± SE)

**PET SUVR (OC)**

Adjusted mean change from baseline (± SE)

Sevigny J et al ADPD Nice 2015
# Next Up for Amyloid Related Phase 3 Trials

<table>
<thead>
<tr>
<th>Small Molecules</th>
<th>Other names</th>
<th>Background</th>
<th>Target Type</th>
<th>Phase 1-2 data in AD</th>
<th>PD effects at selected doses</th>
<th>Clinical POC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALZT-OP1</td>
<td>Cromolyn Na Intal + Ibuprofen</td>
<td>2 FDA approved drugs</td>
<td>Amyloid related inflammation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No phase 1 or phase 2 trials, no PD biomarkers</td>
</tr>
<tr>
<td>Azeliragon</td>
<td>TTP 488 PF 04494700</td>
<td>High dose stopped, + futility analysis in phase 2</td>
<td>Amyloid related inflammation</td>
<td>Available</td>
<td>N/A</td>
<td>N/A</td>
<td>No consistent or clinically meaningful effect on plasma levels of Aβ, or on inflamm biomarkers</td>
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<tr>
<td>Verubecestat</td>
<td>MK8931</td>
<td>Mild to mod AD (n=1960); Prodromal (n=1500)</td>
<td>BACE inhibitor</td>
<td>Phase 2-3</td>
<td>Y</td>
<td>N/A</td>
<td>Dose proportional plasma and CSF exposure and dose dependent lowering of Aβ</td>
</tr>
</tbody>
</table>

1 Sabbagh M et al Alz Dis AssocDis2011, 2 Forman M et al Alz Dement 2013 P69012
AD Drug Development Results 2010-present

Adapted from Mangiolasche F, et al. *Lancet Neurology* July 2010
Regrouping and Refining the Approach

- **Pharmacology matters**
  - First principles: PK, PD, biological effects

- Achieving clinical POC is difficult but needs our creativity to achieve
  - Novel designs, seamless studies, sensitive and ecologically interesting outcome measures

- **Effect sizes: updating our approach to trials**
  - Bigger samples are not necessarily better…….
  - Aim for ES that are clinically important not just statistically significant
  - More programs enabled
    - Investment in more front end costs
  - Attention to the therapeutic product profile
Mobilizing an Adaptive Clinical Trials Platform

Trial Ready Cohort → Master Protocol → Randomization

Run in data Slopes Biomarkers

Common Control Arm

Compound A active arms

Compound B active arms

Compound C active arms

Compound D active arms
Adaptive Trial Design Phase 1

Initial Randomization

Dose A
Dose B
Dose C
Control Arm

Adaptive Randomization

**

Study sample powered for significant results on biomarker primary outcome
Study duration 3-6 months  n=50 tbd
Adaptive Trial Design Phase 2

Initial Randomization

Dose A

Dose B

Dose C

Control Arm

Further Randomization

Clinical outcome**

Study sample powered for significant results on clinical outcome measure
Study duration further 6 – 12 months n=500 tbd
Evolving our Approach

- **Precision medicine:**
  - Intensive analytics around endophenotypes and biomarker panels to predict who may respond
    - Inflammatory endophenotype for an inflammatory therapeutic
    - Metabolic, vascular to specific interventions
  - Novel individualized treatment screening response
    - iPSC cell systems and models to find responders before trials

- **Taking a broader approach to define responders**
  - Including more real world populations
    - comorbid cerebrovascular and other neurodegenerative pathologies
    - Seek responding populations more intensively
    - Adjust designs adaptively
    - Value genetic models for genetic disease but sporadic?
“Skate where the puck is going to be………”

- The Canadian Philosopher
  Wayne Gretzky
Global Alzheimer Platform
New York Academy of Sciences
CCNA and CPAD
EPAD
Don and Scott Berry
Mike Krams

Acknowledgements

Support of the Ralph Fisher and Alzheimer Society of BC Endowed Professorship in Alzheimer’s Research